Clinical trials in MOGAD, NMOSD, and more

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[00:00:05] **Dr. Benjamin Greenberg:** The next talk we're going to have is on clinical trials in MOGAD, neuromyelitis optica spectrum disorder MOG. And it's going to be given by our very own Cindy Wang, who joined us - how many years have you been stuck with us now? It's like a prison sentence. Yeah, exactly. And there's no parole for good behavior. You're still doing your time. So, Cindy came to us for fellowship, and we were very lucky to convince her to stay and join the faculty where she's my partner in crime in the pediatric demyelinating diseases clinic. And has been involved in trying to augment the amount of clinical research and clinical trials we're doing on the pediatric side, something that has historically been done on the adult side, but not quite as well on the pediatric side. So, I'm going to turn things over to Cindy to give us an update on those trials.

[00:01:02] **Dr. Cynthia Wang:** Thank you very much, Dr. Greenberg and thank you to the SRNA for inviting me to talk. These meetings are always so incredible just to meet people and see how our day to day can really impact people. So, with that, I will be talking about clinical trials and MOG antibody disease neuromyelitis optica and MOG. I do not have any relevant financial disclosures. I will say I took a late flight back from Vancouver last night and I'm running on about four hours of sleep, four cups of coffee. And I just finished these slides about an hour ago. So please be kind if I stumble a little bit.

[00:01:45] So the overview for today's talk, I'll talk about initial, what's the purpose? What are definitions when it comes to clinical trials? Talk a little bit about the historical context and what the contemporary treatments for these conditions are. We'll look at what some of the newest and greatest latest clinical trials are in this space. And then I would like to end with highlighting some of the unmet needs which I'm sure many people in the room are very familiar with in a personal level.

[00:02:15] So what is the purpose of a clinical trial? So, thankfully, this is an avenue that can allow people to access new treatments. It's also a way to scientifically and very rigorously study new treatments including the safety as well as the effectiveness. And then some people want to help benefit science or humanity. So that we get better at doing what we're doing as doctors and that patients have more access to effective and safe treatments. You may know how this progresses, but I'll highlight it quickly. There is a phase where there's initial studies in the test tube and in animal models typically, and that's the preclinical stage. Once it moves to humans, the Phase 1 is generally small numbers of healthy people. Just making sure the drug is not toxic.

[00:03:07] The next step is using that drug in people affected with the condition typically in a larger group of people. And looking at other markers such as effectiveness. And by the time, many of people are called to enroll in studies, it's in the three phase which we just want to confirm in a larger group of people. Is this effective? Is this safe? And is this ready to go to market potentially? And now we'll go to some phrases that I'll use in the later slides about the clinical trials that I'll be highlighting. So, what is open label versus blinded? These refer to vision which is a little not lost on people here who've had optic neuritis but open label, you can see what you're getting, it's apparent to you versus blinded. You don't know what you're getting, you could be getting the active drug, you could be getting a placebo. And then if you do get a - if it is unclear what you're going to get we like to - the gold standards is to be blinded. So, you and the investigator do not know what you're getting for objectivity.

[00:04:16] What is placebo control? They alluded to this already. A sugar pill, essentially not an active drug, versus a control. And thankfully, in many of the studies I've seen with NMO and MOG, for some of the treatments, you may be randomized to placebo, but you still can continue some immunosuppressant medications such as mycophenolate was one. These terms have to do with efficacy effectiveness safety. Is it potentially life threatening or very serious side effects versus tolerability? Which may, do you have a headache? Do you have nausea? Do you have fatigue related? I guess the more nuisance type side effects. Pharmacodynamics and pharmacokinetics refer to what the body does to the drug and what the drug does to the body. And I don't know much about those things. Those are pharmacy type things. So, I'll just leave it at that.

[00:05:17] So in the space of these rare immune disorders, we have learned a lot immensely about the different targets. So, with aquaporin-4, we know that it is a protein on astrocyte foot processes. Astrocytes are the supporting cells; they take care of everybody. So, when they're not happy, other cells are not happy. MOG is a part of the myelin sheath. And oligodendrocytes are the cells that make the myelin sheath. And then it's been referred to multiple times that some people have idiopathic, or they have seronegative or doubles seronegative. And we don't know, is that an antibody, is that a different type of immune process? We don't quite know yet. I think that's a group where people are lumped in when we haven't found those things.

[00:06:07] So these are the main conditions I'll talk about. And you'll see here some of the differences, highlighting the targets, the affected tissues. They affect them in different levels of like, I guess prevalence. But usually some combination of optic nerve, spinal cord, and brain and then whether they are relapsing, many people before me have alluded to with MOG, we don't know, maybe half the time it might relapse, but it may be six months from now, it could be 10 years from now. We've seen that in clinic. And then the demographics of these populations tends to be quite different with a female predominance in NMO and more similar numbers female, male in MOG. And then typically older people are affected with NMO. And I'm biased but I feel like children probably equal adults are about the same frequencies as adults.

[00:07:00] It's been amazing the amount of progress that's been made in the last 10 years, or really the last five years when in terms of these FDA-approved treatments, but now there are three FDA-approved treatments for NMO in adults. One of them, I think in the European Union is approved for adolescence. And then right now we don't have any approved MOG treatments. So, when we talk about treatments, I think it's important to think about what phase we're in. The initial phase where you might just be going to the hospital, the ER, they're just trying to rule out the other things that are treated differently. And also look for more common things it could be. And you've heard this fire analogy during the acute illness, people are throwing high dose IV steroids at you or plasma exchange or IVIG just to try to put that inflammation out.

[00:07:50] During the recovery stage, it may be more important to talk about what we do so this doesn't happen again. So, we don't go destroy more of our forest and that's really going to be the focus of the clinical trial that I'll be talking about. But I think equally, if not more important is once you've made it through that

and you're on your chronic immunotherapy, what can you do to help improve your quality of life? And I think that's an area, that certainly is numb, that need. So, I will focus mostly on this area.

[00:08:17] Looking at the historical treatments for NMOSD, in the '90s, early 2000s, we didn't really know it was that much different from multiple sclerosis. Many of the treatments that were tried were multiple sclerosis medications, which was unfortunate because they were either ineffective or potentially harmful and made relapses worse. So, it was later on that groups found that different immunosuppressant medications including Imuran, CellCept, rituximab especially can be really helpful in this condition. So, here's the treatment timeline starting with when Vanda Lennon at the Mayo Clinic discovered the aquaporin-4 for as the target for neuromyelitis optica. There were some initial diagnostic criteria around 2005. During this whole phase, there were the treatments that I had mentioned that were used pretty commonly and then, it was subsequently revised, this criteria, in 2015. And then, as 2019, 2020 came, we had three drugs all very quickly being FDA-approved. And hopefully some of you who have this condition have had access to these.

[00:09:37] The slide is just to show you that, rituximab targets some of the B cells earlier on their maturation. Whereas in inebilizumab or UPLIZNA targets more of the plasma cells plasma, the blast that are making the antibodies. And then looking at other medications satralizumab or Enspryng they block the IL-6 which sometimes helps with keeping these plasma cells churning out those antibodies. And then when you look at the final common end point of the aquaporin-4 antibody, it's this complement system which Eculizumab or Soliris blocks.

[00:10:17] Feel free to prove this at your leisure. I can send you my slides. But I think the main thing I want you to glean from this is that it's incredible that we have three drugs, they all have different mechanisms. They are all very, quite effective. You see these rates of relapse reduction and they have differences in the route of administration, everything from getting an infusion every two weeks to getting infusion every six months. They all have their potential pros and cons as relates to adverse reactions and safety. But I think it does really allow people to have a conversation with their doctor and figure out what could be the best medication for them.

[00:11:01] So all of this progress led Dr. Rost, who was I think the prior chair, perhaps the current chair, I'm not sure of the Science Committee of the American Academy of Neurology to deem 2019 as the year of NMO. So, should we just rest on laurels because did a lot of great things and we can stop there? Well, as a pediatric neurologist, I contend that my patients are not getting access or if they have access, I don't really know the safety hasn't been studied in a formal way in many children. So, I think that is where I will focus some of the talk, especially as pertains to pediatric and MOG trials.

[00:11:44] So I had mentioned that ENSPRYNG in the European Union had been approved for adolescence. So, 12 and up, this study called SakuraSun is looking at the different PKPD safety efficacy tolerability of this in younger population, which is great. It's a Phase 3 study. It's open labels. So, they're only getting active drug and the numbers are much lower as you'll see compared to adults. Eight individuals are what the company hopes to recruit in order to power what they need for the study, and they are currently enrolling. Unfortunately, you have to go to Denver. Fortunately, or unfortunately, depends on your perspective.

[00:12:33] The next medication is inebilizumab. This is the CD19 antagonists. They're looking at PDPK safety Phase 2 open label. That's true for all of these pediatric NMOSD drugs. It's open label. They're going to get active drug. The inclusion criteria is ages 2-17. They do have some requirements in terms of how many attacks that you must have had one attack within the past year or two attacks within two years and be aquaporin-4 positive. They hope to recruit 15 individuals and they will be probably going through that recruitment a little bit longer. Very happily we're going to be a site I think in maybe the next 2-3 months, we

will be able to enroll people. So, it's great to see that we're no longer fly over country to these companies. So, you can go to the coast, or you can come to Dallas. We get a lot of like restaurant awards. So come ask us if you need restaurant recommendations.

[0:13:32] And then this is really exciting because I have patients who are on Soliris, eculizumab, which is a very effective drug. The downside of that drug is you have to get infusions every two weeks and that could be quite difficult if you don't live in an area where they have infusion centers or if you're a child and you don't like to get poked every two weeks. This is looking again at similar things, Phase 2 through 3, open label recruiting 2-17, aquaporin-4 positive, looking to get 12 individuals. Yeah, we tried for this, I think - again, there are many international sites so it's possible a lot of these individuals will be recruited from those, but for the audience here today, those are the locations that will probably be closest to you. And I think Dr. Levy mentioned that they're going to pay for your travel and all those things if you do want to participate. So, please don't let distance be a barrier if that's something you're interested in.

[00:14:39] Now I'm going to shift gears to MOG antibody disease clinical trials. This is rozanolixizumab. I practice this a lot. It was intimidating at first, but then I was like caramel macchiato has the same number of syllables so I can learn this. They're looking at the efficacy and the safety of this medication, Phase 2-3. So now we're shifting into mostly adult studies, which are going to be randomized double blind placebo control because we're at the stage where we don't know as much about MOG. It hasn't proven itself to be entirely relapsing and we don't have great medications that have had more long term like history of being effective. We've only had an ability to test for MOG since about 2015 in the UK, 2017 in the US.

[00:15:36] The age criteria is there above, there have been new proposed diagnostic criteria for MOG. So, you have to meet that criteria. And then again, it's really important that you prove yourself to be a relapsing form of MOG. So at least one documented relapse during the last 12 months prior to enrollment, they hope to get 104 individuals and I guess they hope to do that very quickly. These are the sites in the US and then many more internationally.

Satralizumab is the IL-6 antagonist that has been used and studied in neuromyelitis optica which they have had good data to suggest it might be helpful in MOG as well. This is Phase 3 randomized, line placebo controlled. Interestingly. Or importantly, I should say you can be on some other baseline therapy if you're worried that you might be randomized into the placebo arm. To me, I like that they're looking at adolescence as well as adults. You have to have the confirmed diagnosis of MOG antibody disorder. Either one relapse in the last year or two relapses in the last two years. Hoping to get about 150 individuals in recruiting over the next 3-4 years. So, I had initially presented or what thought I was going to present NMO, MOG, those were the only clinical trials I knew. So, I had to think about, what do I present in this more section?

[00:17:11] And bring you back to this schematic that I had used earlier, this is where a lot of the clinical trials are focused. Once you've recovered from your acute attack, we need to prevent future relapses what we do. Obviously, there's very important work that needs to be done in the other sections, particularly with recovery and symptoms that don't go away after the acute attack has been treated. And then even here, it's only pertinent to you if you have one of these conditions where you have an antibody, you're an adult or you live close to a big city that makes it a lot easier to participate.

[00:17:51] So as I said, I just went to the Child Neurology Society meeting which was in Vancouver, and we had a lot of fun. Here are a few people, including our fellow Linda. I wish she was available today. She has done great work and I think she's actually on her way to Milan Italy. So, we can all feel really bad for her and she's going to go to the MS meeting there. But this was a poster encountered, all these meetings, a lot of students, residents, they do work, and this was something that was done with our competitor, Texas

Children's in Houston. But I think it highlights that there's a lot of things that we haven't really examined that aren't built in as the outcome measures and clinical trials and that might have to do with cognition or mood things that really impact quality of life. So, I was a psychology major in college, and I always had difficulty with this, I think false, dichotomy of what's neurological, what's psychiatric? I think we take care of the same organ. So, I think we need to increase our talk in our discussion of how do we look at these conditions from a more holistic perspective?

[00:19:04] And on that note, there are some trials in the autoimmune brain disorder space, and I'll highlight a couple. Anybody heard of NMDA encephalitis or autoimmune encephalitis? Yeah, I think somebody mentioned brain on fire. So, this is a condition that looks different from the conditions we talked about today. Typically, it doesn't affect the myelin. So, it doesn't immediately show itself on an MRI, but it can lead to a lot of behavioral changes or seizures or even coma. And this is very important condition that we use a lot of the same acute treatments. And they're actually using Uplizna, inebilizumab as the treatment for this condition.

[00:19:49] And then another area of interest I see children including children with neurodevelopmental disorders. Down Syndrome is a very common condition about one in 800 individuals each year who are born and there's this condition that has really emerged in the last probably five years that we've now called Down Syndrome regression disorder. Generally, it's a child with Down Syndrome who is a little bit older outside of the usual age for an autism, like maybe around the age of puberty, but they have this regression where they lose a lot of skills, their speech, their social interaction looks a lot like autism. And there is thought that maybe this could be an autoimmune brain disorder. So, they're looking at things like IVIG and then this medication is called JAK inhibitor.

[00:20:43] And then perhaps these aren't clinical trials, but these are things that people in this room can participate in, which is to help us understand and collect information about all the conditions that we don't have a clinical trial for. So that might be conditions such as acute flaccid and myelitis. If you have optic neuritis but you're double negative, there are networks where you can submit your information. We have been collecting by repository samples here in Dallas. They are a CONQUER program. Kennedy Crier is a spinal cord injury center, and they probably have research, and they can provide assistance and symptom management. Of course, we all are here because of the SRNA.

[00:21:28] And then really all these other organizations have emerged. Some have been around for a long time, some are very new, but I think all of them provide resources to people who get to their side and are very willing to help. So, I will close in the last few minutes talking about unmet needs and what I hope the field will take us in the next few years. So obviously, we need to do better to find biomarkers. If you don't have an antibody, is it because your condition isn't explained by antibodies is in a different part of the immune system that we haven't fully understood? And then for people who have these idiopathic one-time episodes, what can we do to help with our quality of life if relapse isn't something that is going to be part of their future?

[00:22:25] All of this will help us understand the underlying cause of these conditions and then perhaps help with identifying cures. I already said that these chronic residual symptoms, many of you have great questions about the bladder pain spasticity. Those are the day-to-day symptoms that you have to deal with and probably are much more salient to you than anything I've talked about. I think we're looking more at equity and access. So even though these medications are approved, many of them cost hundreds of thousands of dollars. And if you don't have the insurance or they don't have that type of program where you can have access that does it really benefit those people.

[00:23:08] And I'll say that, even though we see a higher amount of potential ethnic minorities with neuromyelitis optica, I think up to like 40% are African or African American in the clinical trials, they probably only represented

about 10% of the participants. So, looking at how we can include those communities and those people that are affected by these conditions. So, I went to University of Michigan for Child Neurology Residency. So, in the time that I graduated, became Dr. Greenberg's fellow, I'm here standing before you today, a lot has changed. And that's really encouraging.

[00:23:54] So I summarized that. Now, there are highly effective and reasonably safe FDA-approved drugs to prevent relapses in your neuromyelitis optica. The caveat is that they're mostly for adults and that there remain cost and access issues. There's an increasing number of pediatric NMOSD studies including our site which will hopefully be recruiting in the next couple of months. But still, that's not that many sites if you don't live near one of our recruitment locations. For children, all these therapies require an IV or some needle and they are only as useful as they are if they continue indefinitely.

[00:24:37] MOGAD clinical trials are underway. And interestingly, there are some therapies including the rozanolixizumab that have a novel mechanism. So how that might help with other conditions. Could that be used for NMO, or can it be used for seronegative NMO? I think is an interesting question. I contend that all of us are in Texas and none of those sites are in Texas, unfortunately. So, I think I have to talk to Ben about why that didn't happen. Mike has conveniently left the room. And they're not recruiting children Under 12.

[00:25:14] I would say like all my ADEM or MOG patients that look like ADEM they're usually in the less than seven- or eight-year range, many optic neuritis patients, they're 8-10 years old. So, we're missing a large population. I know sometimes it's important to do these studies in adults first. But hopefully, those companies are thinking about how children need to be involved in these studies as soon as possible once the safety and the efficacy studies have come out for adults. And then if you don't have an antibody to identify yourself, you're still left out of these studies. I don't want to leave on such a bad note, but I think there's great hope, there's great promise for the future of immune disorders. But I think in order to have real meaningful progress, we have to have a thoughtful way of looking at how we design and implement these clinical trials and research.

[00:26:12] So I will leave you with a couple quotes. If you're in the room obviously you're interested, you're engaged, you have a voice. There are companies that have boots out there, you can talk to them about what your concerns are, and I encourage you to do so. And finally, I want to acknowledge all the people that have allowed us to be here today and for me to have done the training to talk to you about this today, including of course, the SRNA. I was funded with the James Lubin Fellowship. And of course, Sandy and the staff at SRNA you are the heart. And chitter, don't you ever not have him talk at the beginning? Questions?

[00:27:18] **Audience Member 1:** I actually want to go back to the three drugs that are currently approved. It seems that as far as lay people, it's really difficult to understand which one might be best for us based on something which I think is as simple as chance of relapse because they're not terribly long, they weren't big, the protocols were different for all of them. So, it's really hard to do a side-by-side comparison and to make all that sense of that. What would you recommend for us to look at? How do we separate that? Is there any independent paper that's been published that might help us to look at those and really understand why we should pick one over the other?

[00:28:08] **Dr. Cynthia Wang:** Yeah, I think looking at this table, when I talk to my teens, I really try to drill down are you going to be able to - well, I think more with multiple sclerosis or drugs that they have to take a pill, or I have to really rely on them to be compliant. These are all - except for the subcutaneous ones, as long as you can make the infusions, I know you're getting active drug but how feasible is it for you to go to a site where you get infusions every two weeks. Are you working? Is this really going to affect your life? Because I think the effectiveness are all really high and until you are on the drug and you have a relapse, it's really hard to say they haven't been head-to-head studies, and I don't think that's necessarily going to happen.

[00:29:12] And that's a conversation you should have with your neurologist if that's most important, effectiveness more than how cumbersome it is to get the infusions or how the safety or the adverse reactions, and maybe you should start there. But again, we always tell people don't compare those numbers, they're not comparable. And I'll say so many people who have been on rituximab for decades and it's worked for them. We're not asking them to consider these medicines. So, I think again, it's so personal, these decisions. I think probably you have to have a conversation if you pick one that maybe on paper, the numbers might be slightly lower, or the chance of relapse may exist. What can you do in terms of making a plan? Like if I have symptoms, I'm going to go straight in the hospital, I'm going to have a plex catheter placed that day and I'm going to get treatment because now that you know what you have and hopefully other people do too, even if you have a relapse on these conditions, you can mitigate the risk of having disability from subsequent attacks. Any other questions?

[00:30:38] **Audience Member 2:** That is a clinical trial for the NMDAR encephalitis or what? I don't understand how that was coming in.

[00:30:49] **Dr. Cynthia Wang:** It was just to talk about other brain-based conditions that aren't quite thus far under the umbrella of SRNA. They're not typically thought to be like demyelinating conditions. They often have normal MRIs, and the spinal fluid may not be as helpful. But I think it gets to the fact that when we look at other people that have seronegative or idiopathic, they might have different mechanisms. And that was mostly just to highlight that there are other movements to look at immune therapies that target different mechanisms, perhaps like the innate immune system instead of the acquired immune system that makes the antibodies and that T and B cells are involved in. But I don't believe that tofacitinib or any JAK inhibitor is being studied for NMDA autoimmune encephalitis or any of our conditions. Good question. Well, I will let you guys move on.